44. An MRI agent according to claim 22 wherein said peptide binds to said protease.

45. An MRI agent according to claim 22 wherein said peptide is a protease substrate.

46. A method according to claim 30, 32, 33, or 42 wherein said peptide inhibits said protease.

47. A method according to claim 30, 32, 33, or 42 wherein said peptide binds to said protease.

48. A method according to claim 30, 32, 33, or 42 wherein said peptide is a protease substrate.--

REMARKS

Claims 22-48 are pending. Claims 12, 16 and 17 have been cancelled. Claim 22 has been amended to be an independent claim by incorporating the MRI agent formula of claim 12. Claims 42-48 are newly added. Support for new claim 42 is found in the specification at page 20, line 7 through page 21, line 6. Support for new claims 43-48 is found in the specification at page 21, line 7 through page 23, line 16. An Appendix of Pending Claims is attached for the Examiner's convenience.

The priority claim in the application has been amended to clarify the type of applications to which priority is being claimed and to correct a typographical error in the serial number for the PCT application: PCT/US96/08549 to PCT/US96/08548.

Double Patenting Rejections

Claims 12, 16, 17, 22 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent Nos. 5,707,605 and 5,980,862. Claims 12, 16, and 17 have been cancelled and thus the rejection is moot as applied to these claims.

A terminal disclaimer listing U.S. Patent Nos. 5,707,605 and 5,980,862 is enclosed. Applicants respectfully request withdrawal of the double patenting rejection as applied to claims 22 and 23.

Rejection under 35 U.S.C. § 103(a)

Claims 12, 16, and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Garlich et al (U.S. Patent No. 5,133,965) in view of Watson (U.S. Patent No. 5,914,095). Claims 12, 16 and 17 have been cancelled. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 12, 30 and 32 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner states that the claims as written are ambiguous because it is unclear as to what is attached to the COO^- groups. Claims 22 (which incorporates the formula from cancelled claim 12), 30 and 32 have been amended to more clearly indicate that the "-" is not a symbol for a chemical bond, but rather is chemical notation for a negatively charged group, i.e., COO^- (see the specification at page 32, line 6). Applicants respectfully request withdrawal of the rejection.

Claims 24-29, 31 and 33-41 are objected to as being dependent upon a rejected base claim. The Applicants submit that in light of the above amendment and argument, claims 22-41 are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."**

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY, LLP

Dated: 11/20/02

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Filed under 37 C.F.R. § 1.34(a)

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 1, lines 3-9 has been amended as follows:

This application is a continuation-in-part of ~~application of Ser~~U.S. Serial No. 09/134,072, filed August 13, 1998, issued November 9, 1999 as U.S. Patent No. 5,980,862; which is a ~~continuation~~continuation-in-part of ~~Ser.~~U.S. Serial No. 08/971,855, filed November 17, 1997, ~~now~~ abandoned; which claims the benefit of the filing dates~~is a continuation~~ of ~~provisional Ser.~~ U.S. Serial No. 60/063,328, filed October 27, 1997~~; which is a continuation of Ser.~~, closed, and International Application Serial No. US96/08548, filed June 3, 1996, closed, and is a continuation-in-part of U.S. Serial No. 08/486,968, filed June 7, 1995, ~~now~~issued January 13, 1998 as U.S. ~~Pat.~~Patent No. 5,707,605; which is a ~~continuation~~continuation-in-part of ~~Ser.~~U.S. Serial No. 08/460,511, filed June 2, 1995, ~~now~~abandoned. ~~Priority is claimed for PCT No. PCT/US96/08549, filed June 3, 1996.~~

In the Claims:

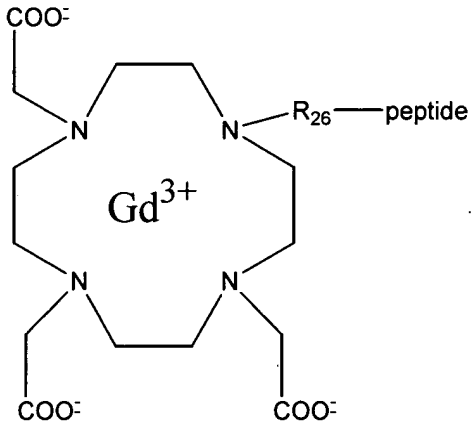
Claim 12 has been cancelled.

Claim 16 has been cancelled.

Claim 17 has been cancelled.

Claim 22 has been amended as follows:

22. (Amended) An activatible MRI agent having [according to claim 12 wherein said target substance is a protease and said peptide inhibits said protease] the formula:

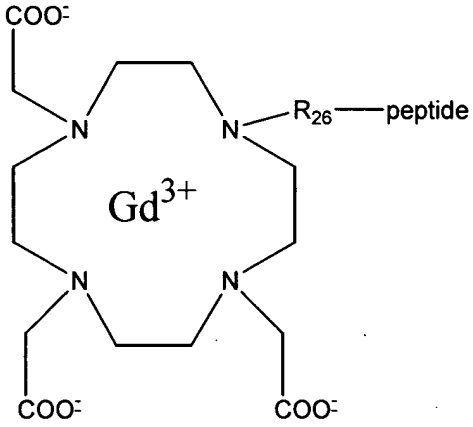


wherein R_{26} is a linker; and,
said peptide inhibits a target substance that is a protease.

Claim 30 has been amended as shown:

30. (Amended) A method [of simultaneously delivering an activatible MRI agent and acquiring an MRI image]comprising:

a) administering an activatible MRI agent to a tissue, cell or patient, said MRI agent having the formula:

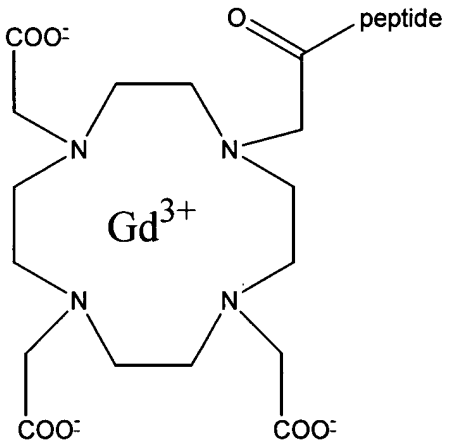


wherein R_{26} is a linker, and under conditions whereby said peptide interacts with a target substance in said tissue, cell or patient such that the rapid exchange of water in at least one coordination site of said agent is increased, and,

b) acquiring a magnetic resonance image of said cell, tissue or patient.

Claim 32 has been amended as shown below:

32. (Amended) A method of according to claim 30 or 42, said MRI agent having the formula:

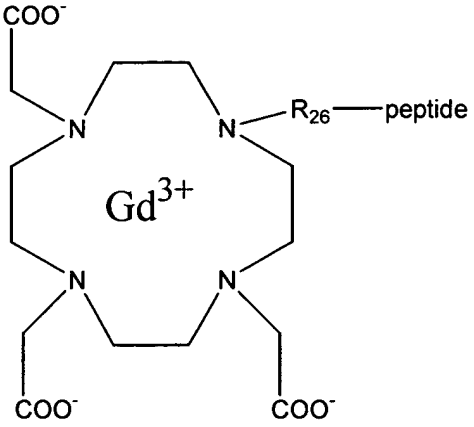


Claim 33 has been amended as follows:

33. (Amended) A method according to claim 30, 32 or 42 wherein said target substance is a protease and said peptide [inhibits] interacts with said protease.

APPENDIX OF PENDING CLAIMS

22. (Amended) An activatible MRI agent having the formula:



wherein R_{26} is a linker; and,
said peptide interacts with a protease.

23. (Amended) An MRI agent according to claim 22 wherein said protease is a caspase.

24. An MRI agent according to claim 22 wherein said protease is an interleukin 1 beta converting enzyme.

25. An MRI agent according to claim 22 wherein said protease is a cysteine protease.

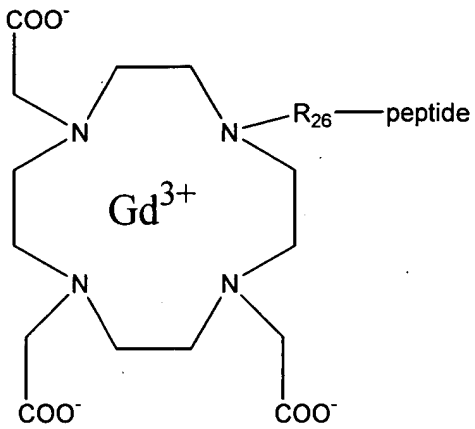
26. An MRI agent according to claim 22 wherein said protease is a serine protease.

27. An MRI agent according to claim 22 wherein said protease is a calpain.

28. An MRI agent according to claim 22 wherein said protease is a cathepsin.

29. An MRI agent according to claim 22 wherein said protease is a metalloproteinase.

30. (Amended) A method comprising:
a) administering an activatible MRI agent to a tissue, cell or patient, said MRI agent having the formula:

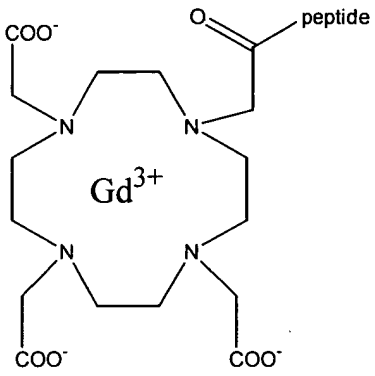


wherein R_{26} is a linker, and under conditions whereby said peptide interacts with a target substance in said tissue, cell or patient such that the rapid exchange of water in at least one coordination site of said agent is increased, and,

b) acquiring a magnetic resonance image of said cell, tissue or patient.

31. A method according to claim 30wherein R_{26} comprises-$((CH_2)CO)$-.

32. (Amended) A method of according to claim 30 or 42, said MRI agent having the formula:



33. (Amended) A method according to claim 30, 32 or 42 wherein said target substance is a protease and said peptide interacts with said protease.

34. A method according to claim 33 wherein said protease is a caspase.

35. A method according to claim 33 wherein said protease is a interleukin 1 beta-converting enzyme.

36. A method according to claim 33 wherein said protease is a cysteine protease.

37. A method according to claim 33 wherein said protease is a serine protease.

38. A method according to claim 33 wherein said protease is a calpain.

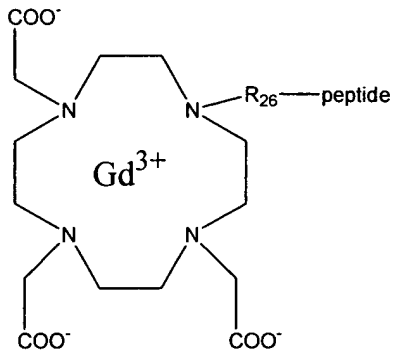
39. A method according to claim 33 wherein said protease is a cathepsin.

40. A method according to claim 33 wherein said protease is a metalloproteinase.

41. A method according to claim 30 comprising administering a composition comprising said agent and a pharmaceutically acceptable carrier.

42. (New) A method comprising:

a) administering an activatible MRI agent to a tissue, cell or patient, said MRI agent having the formula:



wherein R_{26} is a linker, and under conditions wherein said peptide hinders the rapid exchange of water in at least one coordination site;

b) contacting said peptide with a target substance such that the exchange of water in at least one coordination site is increased upon interaction of said peptide with said target substance; and a therapeutic effect is elicited.

43. (New) An MRI agent according to claim 22 wherein said peptide inhibits said protease.

44. (New) An MRI agent according to claim 22 wherein said peptide binds to said protease.

45. (New) An MRI agent according to claim 22 wherein said peptide is a protease substrate.

46. (New) A method according to claim 30, 32, 33, or 42 wherein said peptide inhibits said protease.

47. (New) A method according to claim 30, 32, 33, or 42 wherein said peptide binds to said protease.

48. (New) A method according to claim 30, 32, 33, or 42 wherein said peptide is a protease substrate.